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REVIEW ARTICLE

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Present situation of antimicrobial resistance in Korea

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Abstract Resistance of bacteria to antimicrobial agents is a worldwide concern. In Korea, resistant bacteria are more prevalent than in other industrialized countries. Methicillin-resistant *Staphylococcus aureus*, erythromycin-resistant *Streptococcus pyogenes*, penicillin non-susceptible pneumococci, β-lactamase-producing gonococci, extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*, class C β-lactamase-producing *E. coli*, fluoroquinolone-resistant *E. coli*, and aminoglycoside-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are examples of resistant bacteria prevalent in Korea, and their presence suggests a high level of antimicrobial selective pressure and the nosocomial spread of resistant bacteria. Recently observed rapid increases in the incidence of vancomycin-resistant *Enterococcus faecium* and carbapenem-resistant *P. aeruginosa* present new threats in Korea.

Key words Antimicrobial resistance in Korea · Resistance survey · Nosocomial pathogen

Introduction

It was in the early 1990s that prominent scientists viewed resistance to antimicrobial agents as a crisis and calamity.[1,2] They insisted that the extensive use of antibiotics in the community and hospitals fueled the crisis in antibiotic resistance, which resulted in virtually all pathogenic bacteria becoming resistant to older antibiotics. During the past several years, the antibiotic resistance problem has worsened noticeably in Korea. The increased prevalence of known resistant organisms and the emergence of newly resistant, organisms such as vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*, imipenem-resistant *Pseudomonas aeruginosa*, and fluoroquinolone-resistant gram-negative bacilli, have become of real concern.

The methods used to test antimicrobial susceptibility used may affect the result. In Korea, the majority of laboratories use the disk diffusion method, although some large hospitals use the commercial broth microdilution test. The disk diffusion method used is the only National Committee for Clinical Laboratory Standards (NCCLS) approved method, except for some antimicrobial agents for which NCCLS breakpoints are not available.[3] Most reports on antimicrobial resistance in Korea were based on isolates in large tertiary care hospitals. Therefore, the resistance rates were influenced by the prevalence of nosocomial infections. The analysis of resistance of isolates from outpatients may also fail to show true resistance rates of community-acquired pathogens, as some of the outpatients may have acquired the organisms in hospitals.

Before presenting the current resistance status of some of the more important pathogens, we briefly present the trend of resistance in the recent past in a tertiary care hospital, together with the resistance pattern of *Neisseria gonorrhoeae* from other studies, to show the general picture of resistance in Korea (Figs. 1, 2). Trends show that methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae*, and piperacillin-resistant *Pseudomonas aeruginosa* were already prevalent in the early 1990s, and all of their resistance rates were over 50% in 1999. During this period, VRE, ESBL-producing *K. pneumoniae*, cefoxitin-resistant *E. coli*, imipenem-resistant *P. aeruginosa*, and fluoroquinolone-resistant *E. coli* have emerged and their resistance rates have increased significantly.

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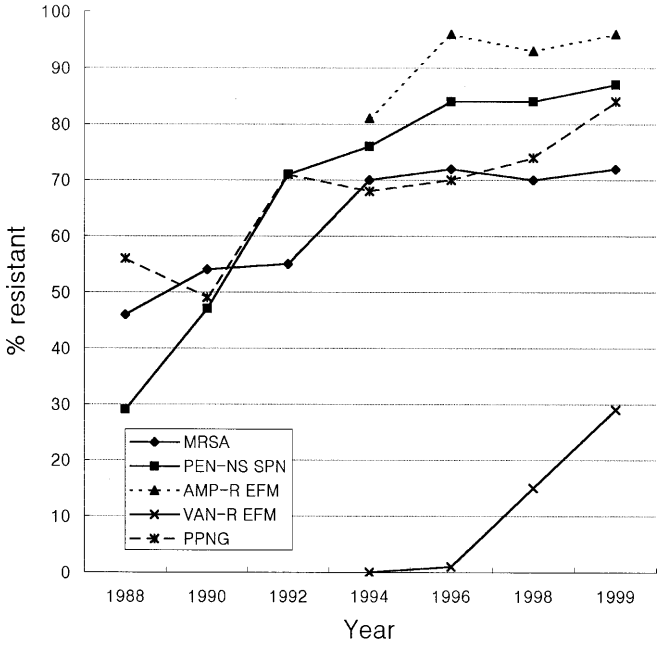

Fig. 1. Trends in antimicrobial resistance of gram-positive and gram-negative cocci between 1988 and 1999 in a tertiary care hospital in Korea. The resistance rates of *Neisseria gonorrhoeae* are cited from other studies. *MRSA*, Methicillin-resistant *Staphylococcus aureus*; *PEN-NSSPN*, penicillin-nonsusceptible *Streptococcus pneumoniae*; *AMP-R EFM*, ampicillin-resistant *Enterooccus faecium*; *VAN-R EFM*, vancomycin-resistant *E. faecium*; *PPNG*, penicillinase-producing *Neisseria gonorrhoeae*

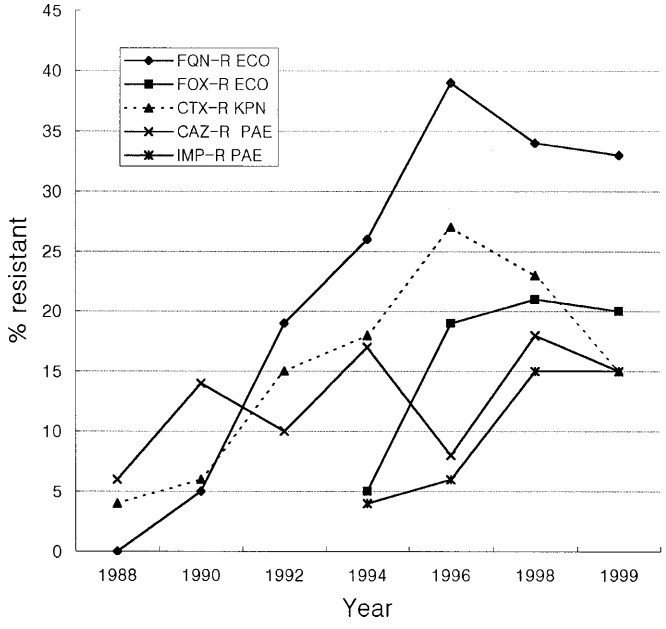

Fig. 2. Trends in antimicrobial resistance of gram-negative bacilli between 1988 and 1999 in a tertiary care hospital in Korea. *FQN-R ECO*, Fluoroquinolone-resistant *Escherichia coli*; *FOX-R ECO*, cefoxitin-resistant *E. coli*; *CTX-R KPN*, cefotaxime-resistant *Klebsiella pneumoniae*; *CAZ-R PAE*, ceftazidime-resistant *Pseudomonas aeruginosa*; *IMP-R PAE*, imipenem-resistant *P. aeruginosa*

Table 1. Antimicrobial resistance rates of important aerobic gram-positive cocci isolated in 1998 in Korea

Species (no. tested)[a]	Antimicrobial agents	Resistance rate (%)
Staphylococcus aureus (26042)	Oxacillin	72
	Clindamycin	63
	Fluoroquinolone	66
	Cotrimoxazole	3
Streptococcus pyogenes (41)	Erythromycin	27
S. agalactiae (40)	Erythromycin	26
S. pneumoniae (2187)	Penicillin non-susceptible	78
Enterococcus faecium (2968)	Ampicillin	80
	Vancomycin	11
E. faecalis (7075)	Vancomycin	0.6

[a] Cited from references 5 and 9; *S. pyogenes* and *S. agalactiae* were isolated in the period 1993–1996

Resistance of staphylococci

S. aureus is an important pathogen, frequently isolated from both outpatients and inpatients with various infections. The increased prevalence of MRSA, a typical nosocomial pathogen, is a serious problem, because it is resistant to all existing β-lactam antibiotics. In Korea, MRSA was not detected in the 1960s. During the period 1971–1979, 3% to 9% of *S. aureus* isolates from blood were methicillin-resistant, but in 1980 the rate was 25%.[4] In the same hospital, the methicillin-resistance rates of all *S. aureus* rose sharply, to 44%, in 1988 and gradually rose again to reach around 70% in 1995. In a 1998 Korean survey, the methicillin resistance rate was found to be 72% (Table 1).[5] In a study of strains from wounds, those isolated in the 1990s were found to be highly resistant, with a methicillin minimum inhibitory concentration for 50% of isolates (MIC_{50}) of 512 μg/ml. It was also noted that the prevalence of coagulase type II increased to 30% and that most were expression class 3 or 4.[6] In Korea, arbekacin is not used, and a 1996 study showed that all of the isolates tested were susceptible to this drug.[7]

The emergence of a vancomycin-resistant (intermediate) *S. aureus* (VISA) in 1996 in Japan, caused new concerns. Studies were undertaken to search for VISA in several Korean hospitals. Kim et al.[8] identified a VISA isolate among MRSAs isolated from a pelvic abscess specimen of a 45-year-old man. However, other workers were not able to

detect any VISA isolates. We screened for the presence of Mu3 type strains, using Mu3 agar, and found that 15% of the isolates showed satellitism around the aztreonam disk. Population analysis demonstrated that they were not VISA strains, but contained subpopulations which were resistant to vancomycin, indicating their potential to become VISA.

Resistance of streptococci and enterococci

In Korea, *Streptococcus pyogenes* remained very susceptible to β-lactam antibiotics, i.e., the MIC of penicillin G was ≤0.015 μg/ml, while the resistance rate to erythromycin was 27% (Table 1) and to that tetracycline was 56%.[9] The resistance rates to these drugs in Korea were much higher than the 2.7% and 16.5% found in Japan during the early 1990s.[10]

S. agalactiae neonatal infection is much less frequent in Korea than in the United States, probably because of the lower genital carriage rate, 5.9%, in Korean pregnant women.[11] The prevalent serotypes remain Ia, Ib, and III, while new serotypes, VI and VIII, have been detected recently.[9] *S. agalactiae* is between five-fold and eight-fold less susceptible to penicillin than *S. pyogenes*. In our study, the MIC range of penicillin G for *S. agalactiae* was 0.03–0.06 μg/ml.[9] The resistance rate to erythromycin was 26% (Table 1) and that to tetracycline was 100%, rates which were much higher than those in Japan in 1986–1992 (i.e., 1.2% and 42%, respectively).[10]

S. pneumoniae is an important pathogen that causes a variety of infections, some of which are serious. The increase in penicillin G-non-susceptible pneumococci has become a serious problem in many parts of the world.[12] The penicillin non-susceptible rate in a Korean tertiary care hospital rose from 3% in 1986 to 29% in 1988, and then increased to 77% in 1993.[13] Similar results have been reported in other hospitals.[14,15] Capsular types 19F and 23F were frequently isolated, and these types of isolates were often non-susceptible to penicillin G. A Korean nationwide survey in 1998 showed the mean penicillin non-susceptible rate to be 78% (Table 1), which was much higher than the 52% reported in Japan during 1994–1995.[16]

Enterococci became more frequently isolated from inpatients, and the proportion of *Enterococcus faecium* increased to 38% of all enterococci in Korean tertiary hospitals. The ampicillin-resistance rate of *E. faecalis* is very low, but the ampicillin-resistance rate of *E. faecium* was 80% in 1998 (Table 1), and 96% in 1999 in a tertiary care hospital (Fig. 1). Although most enterococci were isolated from urine specimens, some were isolated from blood specimens. As enterococci are inherently less susceptible to β-lactam antibiotics, enterococcal endocarditis is treated with aminoglycoside combinations. However, a gradual increase in high-level aminoglycoside-resistant isolates has been noted. In a Korean tertiary care hospital in the period 1991–1992, high-level resistance rates to gentamicin were 20% in *E. faecalis* and 59% in *E. faecium*.[17] In another study, the resistance rates to gentamicin and streptomycin were: *E. faecalis*, 61% and 39%, respectively; and *E. faecium*, 45% and 55%, respectively.[18]

The first isolation of VRE in Korea was reported in 1992,[19] but it was rare. In a tertiary care hospital, among the 31 *E. faecalis* and 11 *E. faecium* strains isolated from blood during the period 1996–1998, only one isolate of *E. faecium* was resistant to vancomycin.[18] However, in another tertiary care hospital, the proportion of vancomycin-resistant *E. faecium* started to rise sharply in 1998 (Fig. 1) and reached 29% in 1999. Most of the VRE were *E. faecium* of type VanA. Pulsed-field gel electrophoresis (PFGE) patterns suggested that both the clonal and the horizontal spread of resistance were the cause of the sharp increase. Donskey et al.[20] noted that it was difficult to control the spread of VRE by infection control measures alone.

Resistance of *Neisseria* and *Moraxella*

Low-level penicillin G-resistant isolates of *N. gonorrhoeae* were already prevalent in Korea in the 1960s, but a penicillinase-producing strain (PPNG) was first reported in 1979. In the 1990s, almost all isolates were resistant to penicillin G, either by chromosomal resistance or by β-lactamase production (Table 2). Since the early 1990s, the proportion of PPNG has been to over 70% (Fig. 1).[21,22] However, the isolates remained highly susceptible to ceftriaxone, i.e., the MIC range was ≤0.008–0.06 μg/ml. A recent decrease in PPNG in other countries is probably related to the increase in quinolone-resistant strains, as reported in Hong Kong.[23] In Japan, the ciprofloxacin resistance rate of gonococci isolated in the period 1997–1998 was

Table 2. Antimicrobial susceptibility of gonococci isolated in 1997–1999 in Korea

Antimicrobial agents	Strains (no. tested)	MIC range (μg/ml)	Percentage of isolates		
			Susceptible	Intermediate	Resistant
Penicillin G	Non-PPNG (29)	0.12–1	0	100	0
	PPNG (144)	2–>128	0	0	100
Ciprofloxacin	Non-PPNG (29)	≤0.008–0.5	59	41	0
	PPNG (144)	≤0.008–1	35	64	1
Tetracycline	All (173)	1–8	0	13	87

MIC, Minimum inhibitory concentration; PPNG, penicillinase-producing *Neissseria gonorrhoeae*

23.6%,[24] while the ciprofloxacin resistance rate of PPNG was only 4% in 1994.[25] In Korea, isolates of gonococci often showed intermediate resistance to ciprofloxacin (i.e., MICs were ≤1 μg/ml) until 1999, but high-level resistant isolates started to be isolated in 2000. Spectinomycin-resistant gonococci remained rare, as was reported in other Asian countries.[25] *Moraxella* (*Branhamella*) *catarrhalis* is not frequently isolated from clinical specimens in Korea. Studies showed that approximately 95% of recent isolates were producing β-lactamase.

Resistance of gram-negative bacilli to β-lactams

Enterobacteriaceae and glucose-nonfermenting gram-negative bacilli are frequently isolated from various community-acquired and nosocomial infections. Some of the current resistance problems with *Enterobacteriaceae* are an increase in the numbers of ESBL- or AmpC β-lactamase-producing strains of *E. coli* and *K. pneumoniae*, and increases in AmpC β-lactamase-hyperproducing strains of *Enterobacter*, *Citrobacter*, and *Serratia* spp. In a Korean survey in 1998, which involved 25 hospitals, resistance rates of *E. coli* were 78% to ampicillin and 44% to cephalothin (Table 3). Cefotaxime resistance rates, determined by regular NCCLS breakpoint, were 8% for *E. coli* and 22% for *K. pneumoniae*. Therefore, ESBL-producing strains must be more prevalent than what is shown by the above rates. In a hospital, the rates of cefotaxime-susceptible *E. coli* and *K. pneumoniae* decreased from 99% to 89% and from 94% to 70%, respectively, during the period 1986 to 1993.[26] Among the non-susceptible isolates, 69% of *E. coli* and 76% of *K. pneumoniae* were double-disk synergy-positive, indicating that they were ESBL producers. It was reported that ESBL-producing *E. coli* and *K. pneumoniae* were isolated only from nosocomially infected patients, which indicated that they were nosocomial pathogens.[27] In a tertiary care hospital in 1999, resistance rates of isolates from inpatients and outpatients were: *E. coli* for cefotaxime, 23.6% vs 2.5%; and ceftazidime, 7.9% vs 1.7%; *K. pneumoniae* for cefotaxime, 17.5% vs 2.3%; and ceftazidime, 31.7% vs 3.6%. These findings suggest that the nosocomial spread of ESBL-producing strains is a significant cause of their high prevalence.

It was reported that, of five ESBL-producing isolates, four produced TEM-type and 1 produced SHV-type enzymes.[28] Pai et al.[29] reported that the most prevalent ESBL types of *K. pneumoniae,* isolated at three university hospitals, were SHV-2, and SHV-12a, and TEM-52 types were reported later. It is interesting that Toho- and Kitasato-type ESBLs, found in Japan, have not yet been detected in Korea.

Since 1989, over 15 plasmid-encoded AmpC β-lactamases have been reported worldwide.[30] A class C β-lactamase, CMY-1, was first identified from *K. pneumoniae* in Korea in 1988. Bauernfeind et al.[31] reported that CMY-1b had an amino acid change from Asn at position 346 of CMY-1a to Ile, resulting in increased resistance to ceftazidime. A survey in 1998 showed that 12% of *E. coli* and 14% of *K. pneumoniae* were resistant to cefoxitin.[5] Pai et al.[29] reported that AmpC β-lactamase was detected in 8 of 57 *K. pneumoniae* isolates. Among the cefoxitin-resistant *E. coli* and *K. pneumoniae*, 6 of 19 and 3 of 7, respectively, had the conjugatively transferable CMY-1 β-lactamase gene.[32]

Enterobacter, *Citrobacter*, and *Serratia* spp. frequently cause nosocomial infections and are often resistant to third generation cephalosporins. In the 1998 survey, in Korea 47% and 51% of *E. cloacae* and *S. marcescens*, respectively, were resistant to cefotaxime (Table 3);[5] resistance rates to ceftazidime were 48% and 25%, respectively. Cefepime is

Table 3. Antimicrobial resistance rates of *Enterobacteriaceae* and glucose-nonfermenting gram-negative bacilli isolated in 1998 in Korea

Antimicrobial agents	Percentage of isolates resistant (no. tested)[a]					
	E. coli (20,604)	*K. pneumoniae* (9079)	*E. cloacae* (5781)	*S. marcescens* (3324)	*A. baumannii* (11866)	*P. aeruginosa* (20370)
Ampicillin	78	NT	NT	NT	NT	NT
Aminopenicillin/sulbactam or clavulanic acid	29	25	67	93	14	NT
Piperacillin	61	35	54	38	75	43
Piperacillin/tazobactam	5	10	35	37	43	35
Cephalothin	44	38	NT	NT	NT	NT
Cefotaxime	8	22	47	51	83	NT
Ceftazidime	7	25	48	25	64	17
Cefoxitin	12	14	97	74	98	NT
Cefotetan	5	4	57	9	82	NT
Imipenem	0	0	0.8	1	5	17
Amikacin	5	9	16	20	60	30
Gentamicin	32	28	47	48	79	50
Tobramycin	25	32	51	62	78	48
Fluoroquinolone[a]	25	8	16	22	71	42

NT, Not tested

[a]Tested either by ciprofloxacin, levofloxacin, or ofloxacin

active against class C β-lactamase-producing isolates. In 1991, it was reported that all isolates of *Enterobacteriaceae* tested were susceptible to cefepime,[33] and in 2000 in a tertiary care hospital, cefepime-resistant isolates remained rare, i.e., 1% each for *E. coli* and *E. cloacae* and 2% for *K. pneumoniae* and 4% for *S. marcescens*; none of the other species of *Enterobacteriaceae* were resistant.

Imipenem is the most active β-lactam drug against gram-negative bacilli, including *P. aeruginosa* and *Acinetobacter baumannii*. Imipenem-resistant *P. aeruginosa* and other gram-negative bacilli with IMP-1 β-lactamase-production were reported in Japan.[34] This report was followed by others of carbapenemase-producing *P. aeruginosa* and *A. baumannii* in Italy, Greece, and France.[35] In a Korean hospital, the imipenem-resistance rates of *P. aeruginosa* were 3% to 6% during the period 1994–1996, but in the period 1997–1999, the rates rose to 14%–15%. This tendency was also observed in other Korean hospitals. Some of this resistance was due to a decrease of outer membrane protein, but 8.7% of the imipenem-resistant isolates produced carbapenemase.[36] Interestingly, the polymerase chain reaction showed that the carbapenemase was not an IMP-type, but a VIM-type β-lactamase. It is of great concern that carbapenem resistance in Korea is increasing and that it is transferable by conjugation.

Resistance of gram-negative bacilli to fluoroquinolones and aminoglycosides

Ciprofloxacin, ofloxacin, and levofloxacin are fluoroquinolones that are very active against gram-negative bacilli, including enteric pathogens; however, increasing resistance is a worldwide concern.[37] In a Korean hospital, only 5% of *E. coli* and 1% of *K. pneumoniae* were resistant to ofloxacin in 1991, but these rates rose rapidly, to 26% and 19%, respectively, in 1994. The resistance rate of *E. coli* to the fluoroquinolone was 33% in 1999 (Fig. 2). The 1998 survey showed that resistance to the agent was more prevalent in large hospitals (defined as those with 1000 or more beds) compared with other hospital size categories), particularly in *E. coli* (Table 4).[5] In a tertiary care hospital in 1999, the fluoroquinolone resistance rates of isolates from inpatients and outpatients were: *E. coli*, 39.8% vs 19.4%; *K. pneumoniae*, 13.8% vs 1.6%. These results suggest the presence of nosocomial infections with fluoroquinolone-resistant *E. coli* and *K. pneumoniae*, together with existence of fluoroquinolone-resistant *E. coli* in the community. The fluoroquinolone resistance rates of *P. aeruginosa* and *A. baumannii* in the 1998 survey were 24% to 39% and 23% to 58%, respectively, depending on the hospital size category.

The aminoglycoside-resistance pattern in the Far East was reported to differ from that in the United States.[38] In 1998, the amikacin resistance rates of *E. coli* and *K. pneumoniae* in Korea were relatively low, at 5% and 9%, respectively (Table 3), but the rates for *E. cloacae* and *S. marcescens* were 16% and 20%, respectively, and rates were much higher for *A. baumannii* and *P. aeruginosa*, at 60% and 30%, respectively. Gentamicin resistance rates were 32% for *E. coli*, 28% for *K. pneumoniae*, 48% for *S. marcescens*, 79% for *A. baumannii*, and 50% for *P. aeruginosa*. Tobramycin resistance rates were similar to those for gentamicin.

Resistance of *Salmonella* and *Shigella*

Ampicillin-resistant non-typhoidal *Salmonella* was rare in Korea until the early 1980s, i.e., only 4 of 211 isolates were resistant during the period 1979–1983. In 1986, 65% or more of *Salmonella* serovar Typhimurium were resistant to ampicillin, chloramphenicol, or tetracycline.[39] In another study, 36% of *Salmonella* Typhimurium were resistant to ampicillin,[40] and this rate was similar to that in Japan.[41] During the period 1995–1997, 5 strains of nontyphoidal *Salmonella* were isolated which produced TEM-52 ESBL.

Typhoid fever was prevalent until the early 1980s in Korea, but, since the early 1980s, the isolation of *Salmonella* Typhi has rapidly decreased and non-typhoidal *Salmonella* has increased. Antibiotic-resistant *Salmonella* Typhi was not known to exist until an isolate was detected in 1992 from a patient who had traveled to South East Asian countries. Two resistant isolates were again isolated at the same hospital in 1995. In 1997, 11% and 15% of the isolates collected by the National Institute of Health Korea were resistant to ampicillin and chloramphenicol, respectively.[40]

Bacillary dysentery was very prevalent in the past, but now it occurs much less frequently. It was reported that, among the *Shigella* strains isolated in 1998, 8% were *S. flexneri* and 92% were *S. sonnei*.[42] *S. flexneri* is well known for its antimicrobial resistance. Among the *S. sonnei* isolates in 1998, 99% were resistant to cotrimoxazole and 71% were resistant to ampicillin.

Resistance of *Haemophilus influenzae* to β-lactams

H. influenzae is a frequent causative agent of bacterial meningitis. In the early 1980s, 9% of *H. influenzae* isolates in Korea were resistant to ampicillin, by β-lactamase production.[43] The rate gradually rose, and in the 1998 survey, it was 56%,[5] a rate that was much higher than that reported in the United States (34% in 1993–1997[44]) and that reported in Japan (13.3% in 1996–1998[45]). In the 1998 survey, β-lactamase-positivity rates of *H. influenzae* were similar in large and medium (less than 1000 beds) hospitals (Table 4). β-Lactamase-negative ampicillin-resistant (BLNAR) strains and β-lactamase-positive aminopenicillin/clavulanate-resistant (BLPACR) strains exist in Japan, but such strains have not been studied in Korea, as yet.

Table 4. Comparison of resistance rates of some bacterial species, by hospital categories, in 1998 in Korea

Species	Antimicrobial agents	Percentage of resistant isolates in hospital categories[a]			
		Large	Seoul – medium	Non-Seoul – Medium	Mean
S. aureus	Oxacillin	73	73	70	72
S. pneumoniae	Penicillin	84	81	71	78
E. faecium	Ampicillin	82	80	77	80
	Vancomycin	8	14	10	11
E. faecalis	Vancomycin	0.8	0.5	0.6	0.6
E. coli	Cefotaxime	10	6	8	8
	Cefoxitin	14	13	9	12
	Fluoroquinolones	29	21	25	25
K. pneumoniae	Cefotaxime	27	28	11	22
E. cloacae	Cefotaxime	55	36	44	47
P. aeruginosa	Ceftazidime	18	17	16	17
	Imipenem	15	21	14	17
H. influenzae	Ampicillin	60	58	56	58

[a] Hospital categories: large, ≥1000 beds; medium, <1000 beds

Resistance of *Bacteroides fragilis*

Among the anaerobic bacteria, the *Bacteroides* species often cause infections. Only 1% of *B. fragilis* isolated in Korea in the period 1995–1996 showed resistance to cefoxitin, but the clindamycin resistance rate was 43%, a rate much higher than that in other countries.[46] During the period 1989–1996, none of the isolates of *B. fragilis* were resistant to imipenem, metronidazole, or chloramphenicol, but the resistance rates to piperacillin and cefotaxime during this period rose markedly, from 12% to 25%, and from 17% to 33%, respectively. In general, the resistance rates of the non-*fragilis B. fragilis* group species were higher than those of *B. fragilis*.

In summary, methicillin-resistant *S. aureus*, erythromycin-resistant *S. pyogenes*, penicillin non-susceptible pneumococci, β-lactamase-producing gonococci, ESBL-producing *E. coli* and *K. pneumoniae*, class C β-lactamase-producing *E. coli*, fluoroquinolone-resistant *E. coli*, and aminoglycoside-resistant *A. baumannii* and *P. aeruginosa* are more prevalent in Korea, at higher rates than in other countries; this suggests the presence of high levels of antimicrobial selective pressure and the nosocomial spread of resistant bacteria. The recently observed rapid increases in vancomycin-resistant *E. faecium* and carbapenem-resistant *P. aeruginosa* present new threats in Korea.

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